REMARKS

Claims 3-8, 10, 12, 15-17, 25, 35-53 and 55 are pending. Applicants elect Group I (claims 3-4 and 17) for examination on the merits, with traverse. Applicants reserve the right to prosecute nonelected subject matter in a further patent application.

Reconsideration of the restriction requirement is requested.

Traversal is based on the lack of a showing that examining claims of both Groups I and II would constitute an undue burden. Applicants submit that Group II (claims 5-8) are directed to methods of making the isolated complex described in Group I (claims 3-4).

Moreover, Applicants respectfully request that Group III (claims 10 and 12) and Group XI (claim 55) be joined with Group I. Applicants urge that restriction is improper since it restricts into separate groups claims that are directed to related chemical compounds. The claimed chemical compounds of claims 3-4, 10, 12, 17 and 55 (Groups I, III and XI) are clearly related as each shares a high degree of sequence identity, a common structure, and have related properties.

The Examiner asserts, "Inventions I, III and XI are unrelated . . . . they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects" (Office Action, page 3). The assertion is ill conceived. It is clearly described in the specification that chemical compounds of the claims of Groups I, III and XI are parts of the same biochemical pathway. The proteins from the library claimed in Group XI are cleaved from fragments claimed in Group III, which are later conjugated to ubiquitin to form compounds claimed in Group I.

The functional and structural relationship between activated fragments and conjugates is clearly disclosed in the specification:

> One specific example of an important ubiquitylation pathway is N-End rule ubiquitylation, and especially N-End rule ubiquitylation where ubiquitylation is preceded by N-terminal segment cleavage, where the N-terminal segment comprises one or more amino acid residues. The proteolysis exposes an N-degron which comprises a destabilizing N-terminal residue plus an internal Lys residue where a multi-Ub chain is later attached. The N-terminal segment is cleaved to form an activated

> substrate of the Ub-dependent N-end rule pathway (activated fragment) which is recognized through exposed destabilizing N-terminal residue.

Page 4 of the specification.

For Example, claim 10 (Group III) is directed to a "fragment of a protein" where a protein is selected from a group of ten sequences identified by their conventionally used names in the claims and by IMAGE ID numbers in the specification while claim 3 (Group I) is directed to an ubiquitin conjugate of a protein selected from an identical group "**and fragments and derivatives thereof**" including fragments of claim 10. Claim 55 (Group XI) is directed to the library of ten specific sequences identified by the names commonly used in the art in the claims and by their IMAGE ID numbers in the specification. These sequences are selected based on their ability to be cleaved by proteases to form activated fragments of claims of Group III and to be conjugated to ubiquitin of the claims of Group I.

Where there is a relationship disclosed between species, such disclosed relation must be discussed and reasons advanced leading to the conclusion that the disclosed relation does not prevent restriction, in order to establish the propriety of restriction. See M.P.E.P. § 808.01(a). The Examiner has not provided the required discussion and did not advance reasons supporting the proposed restriction.

The M.P.E.P. § 803 states:

> For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in M.P.E.P. § 808.02.

Thus, the Examiner has failed to establish a *prima facie* showing because only one field of search is required due to the close relationship between the compounds. The Examiner will search for protein names or IMAGE ID numbers. This search will simultaneously encompass the ubiquitin conjugates of the N-end rule ubiquitylation substrates (Group I), activated fragments of these proteins (Group III) which are intermediates on the way to the complexes claimed in Group I, and the library of N-end rule ubiquitylation substrates (Group XI).

Furthermore, Applicants respectfully request that Group V (claims 25 and 35-39) be joined with claims of Groups I, III and XI. The claims are merely related to the methods for identifying active compounds which modulate the levels of the ubiquitin-protein conjugate of Group I (claims 3-4 and 17) or the levels of a compound of Group III (claims 10 and 12). Contrary to the Examiner's assertion on page 3 of the Action, the methods of claims 25 and 35-39 can clearly be used together with compounds of the claims of Groups I and III. Furthermore, identification of these compounds will necessarily lead to the search for the method for determining the mechanism of the compound's action. Thus, the rejoinder of Group VI (claims 40-41) is also respectfully requested.

In view of the relationship between these groups, Applicants maintain that examination of Groups III, IV, V, VI and XI along with elected Group I would not impose an undue burden on the Examiner. In particular, a search for art related to the subject matter of Group I would encompasses the subject matter of Groups III, IV, V, VI and XI and *vice versa*. Accordingly, to require the filing of a separate divisional application directed to each of Groups III, IV, V, VI and XI would result in the very same search for art being repeated. Such duplicate effort would be inefficient to the operation of the Patent Office. Furthermore, it is likely that the same Examiner would be in charge of the divisional applications, but since the divisional applications would be examined at a later date, the Examiner would have to conduct duplicate, redundant art searches for the divisional applications.

Moreover, as a result of the GATT legislation limiting the term of a patent to twenty years from its effective filing date, the delay in the examination of the non-elected claims likely would result in the patent term for these claims being unnecessarily shortened.

Therefore, since the outcome of the present restriction requirement would be to delay the examination of the claims of Groups III, IV, V, VI and XI, resulting in inefficiencies and unnecessary expenditures by Applicants, and since a single search can be performed for all the subject matter defined by the claims in Groups I, III, IV, V,

VI and XI without any significant burden on the Patent Office, Applicants respectfully request reconsideration and withdrawal of the restriction requirement so that Groups I, III, IV, V, VI and XI are examined on the merits together in the instant application.

Therefore, Applicants submit that the restriction requirement is improper and should be withdrawn. The rejoinder of the Groups III, IV, V, VI and XI with Group I which represents claims 3-4, 10, 12, 15-17, 25, 35-41 and 55 is respectfully requested.

Under the Commissioner's Notice of March 26, 1996 (1184 OG 86) implementing the Federal Circuit's decisions of *In re Ochiai*, 37 USPQ2d 1127 (1995) and *In re Brouwer*, 37 USPQ2d 1663 (1996), rejoinder of process claims is requested upon an indication that a product claim is allowable.

Applicants respectfully reserve the right under M.P.E.P. § 821.04 to rejoin with Group I (claims 3-4 and 17):

- claims 5-8 of Group II as directed to producing compounds of claims 3-4 and 17; or
- claim 49 of Group VIII as directed to changing the level of the precursor protein for complex of claims 3-4; or
- claims 50-52 of Group IX as directed to modifying precursor proteins for complexes of claims 3-4; or
- claim 53 of Group X as directed to generating a phenotypic cell line which contains compounds of claims 3-4;

if the product claims are deemed patentable.

Further, if the claims of Group III are deemed patentable, Applicants reserve the right under M.P.E.P. § 821.04 to rejoin Group III (claims 10 and 12) and Group IV (claims 15 and 16) with claims directed to producing the compounds of claims 10 and 12.

Applicants respectfully reserve the right under M.P.E.P. § 821.04 to rejoin Group V (claims 25 and 35-39) and Group VIII (claims 42-48) with claims directed to producing a pharmaceutical composition based on compounds identified by the methods of claims 25 and 35-39, if the claims of Group V are deemed patentable.

Applicants earnestly solicit an early and favorable examination on the merits. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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